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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/745,226	12/21/2000	Robert A. Herrmann	4010.9	7530

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EXAMINER
MCINTOSH III, TRAVISS C

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 08/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/745,226	HERRMANN ET AL.	
	Examiner	Art Unit	
	Traviss C McIntosh	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-48,50-56 and 58-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-48, 50-56, and 58-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5)☐ Notice of Informal Patent Application (PTO-152)

3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6)☐ Other

DETAILED ACTION

The Amendment filed May 27, 2003 has been received, entered into the record, and carefully considered. The following information provided in the amendment affects the instant application by:

Claims 1-32, 49, and 57 have been canceled.

Claims 38 and 42 have been amended.

Remarks drawn to rejections of Office Action mailed February 25, 2003 include:

Specification objection: which has been withdrawn due to applicant's amendment.

112 1st paragraph rejection: which is maintained for reasons of record.

112 2nd paragraph rejections: which have been overcome by applicant's amendments and have been withdrawn.

103(a) rejections: which have been maintained for reasons of record.

An action on the merits of claims 33-48, 50-56, and 58-70 is contained herein below. The text of those sections of Title 35, US Code which are not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 50-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the various disorders, does not reasonably provide enablement

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

Claims 50-54 are drawn to methods of treating and preventing various conditions, including atherosclerosis, myocardial infarction, restinosis, stroke, impotence, cancer, bacterial infection, impetigo, psoriasis, pruritis, and warts, comprising administering a drug delivery system comprising a lipid molecule derivatized to comprise a nitric oxide releasing group.

The state of the prior art

Nitric oxide is known to play a central role in diverse processes, such as host defense, cardiovascular regulation, signal transduction, neurotransmitting, and wound healing, as seen in US 5,519,020. Nitric Oxide is known to inhibit the aggregation of platelets, as seen in US

seen in US 5,814,666. At present, there are no known agents capable of preventing all of the various conditions, including cancer as applicant asserts in their method claims. The standard for prevention is high, and requires evidence commensurate in scope and correlative to prior art teachings.

The level of predictability in the art

The examiner acknowledges the probability and predictability that the active agent, which is nitric oxide, indeed has efficacy in treating the various disorders. However, the art is silent with regard to the predictability of the prevention of the various conditions, i.e. cancer. In fact, the art does not teach the prevention of cancer by any compounds or active agents. There is not seen to be sufficient data to substantiate the assertion that the various conditions may be prevented by the use of a nitric oxide releasing compound. One skilled in this art would not predict from the disclosure provided that these various conditions can be prevented in view of the data and examples provided, the silence of such predictability in the art and the lack of disclosures providing guidance or support for prevention of any disease or condition.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to enable the use the claimed method commensurate in scope with the instant claims. There is no data and there are no examples which adequately represent the scope of the claims as written. The examiner notes that there has not been provided sufficient instruction or sufficient methodological steps and procedures to support the alleged efficacy of the system as a preventive agent instantly asserted.

There are no examples in the instant application which are seen to provide support for predicting the prevention of any disease or condition.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the prevention of the various conditions without undue experimentation.

Reasonable guidance with respect to prevention, especially preventing cancer, relies on quantitative analysis from defined populations which have been successfully prescreened and are predisposed to particular types of the specific conditions. This type of data might be derived from a widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance for the specific condition and to *link* those results with a subsequent histological confirmation of the presence or absence of the disease. This irrefutable link between antecedent drug treatment and subsequent knowledge of the prevention is the essence of verification of a valid preventive method.

In the amendment filed May 27, 2003 applicants argue that "in view of the alternative nature of the claim language, it is respectfully submitted that the claims are enabling. In this connection, it is noted that claims can embrace some inoperative embodiments while still meeting the requirements of 35 USC § 112, first paragraph". The examiner respectfully disagrees. As set forth in the MPEP, 2164.08, titled "Enablement Commensurate in Scope With the Claims" reads:

> All questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims. The examiner should determine what each claim recites and what the subject matter is when the claim is considered as a whole, not when its parts are analyzed individually. No claim should be overlooked. With respect to dependent claims, 35 U.S.C. 112, fourth paragraph, should be followed. This paragraph states that "a claim in a dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers" and requires the dependent claim to further limit the subject matter claimed.
>
> The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation'." *In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).* Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art.

Thus, the claims are not enabled for the full scope of that which applicants intend, and therefor the rejection under 35 USC 112 2nd paragraph is maintained.

Claim Rejections - 35 USC § 103

Claims 33-48, 50-52, 56 and 58-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler et al. (US Patent 5,770,645) in view of Garfield et al. (US Patent 5,698,738).

The claims of the instant invention are drawn to a drug delivery system comprising a medical article and a nitric oxide (NO) releasing compound. The NO releasing compound of the instant invention comprises a lipid molecule (any of phosphoglycerides (phosphatidylinositol or phosphatidylcholine), those having a sphingosine base as a backbone (N,N,N-trimethylsphingosine, a sphingolipid, or ganglioside), monoacylglycerides, diacylglycerides, glycosylacylglycerols, or sterols having the formula as in claim 33 of the instant (cholesterol)) comprising a S-nitroso, O-nitroso, or N-nitroso group. The medical article can be a bandage, patch, or intravascular medical device (balloon catheter, injection catheter, infusion catheter, a stent, a stent graft, or a distal protection device). The NO releasing compound may be in a polymer matrix, dissolved or dispersed in a solution, provided within a micelle or liposome, adsorbed on the tissue-contacting surface of the medical article, and additionally comprise an additional therapeutically effective agent. The instant application is additionally drawn to a method of administering NO to a patient comprising administering the drug delivery system to the patient. The drug delivery system may be administered topically, within the body, by implantation or an intravascular delivery device (balloon catheter, injection catheter, infusion catheter, a stent, a stent graft, or a distal protection device). Additionally claimed is a method of treating atherosclerosis, myocardial infarction, restinosis, peripheral vascular disease, stroke,

impotence or septic shock in a patient comprising administering the drug delivery system to a patient.

Stamler et al. (Stamler) teach of polymers capable of delivering NO to a patient. NO is taught to inhibit platelet aggregation, reduce smooth muscle proliferation, reduce restinosis, thrombus formation, and to be an anti-inflammatory (column 1, lines 22-31). The polymer of Stamler has pendant S-nitroso and/or O-nitroso groups obtained by reacting a polythiolated polysaccharide with a nitrosylating agent or a nitrating agent under conditions suitable for nitrosylating or nitrating free thiol groups (column 2, lines 34-40). The polymers are coated on a medical device, which is then implanted into the patient, or for delivering NO to a bodily fluid, the bodily fluid is contacted with the coated medical device (column 2, lines 50-57). Suitable polymers which are to be nitrosylated for NO delivery include synthetic and natural polymers (polysaccharides or peptides) and can be hydrophobic or hydrophilic (column 3, lines 48-58). NO is connected to the polymers of Stamler via a linking group, which is preferably S, O, or N (column 4, lines 12-22). The NO delivering polymer of Stamler is prepared by reacting a polysaccharide having a pendant alcohol group with a thiolating reagent to form a thiolated polysaccharide, thereby reacting thiolated polysaccharide with nitrosylating agent to form a nitrosylated polysaccharide (column 6, lines 17-62). Stamler teach the polymer may be in a polymer matrix (column 7, lines 37-45). Stamler additionally teach that coated stents may be examples of medical devices used for implantation (column 10, lines 5-62).

What is not taught by Stamler is to use lipids as the core molecule which will ultimately release NO.

Garfield et al. (Garfield) teach that decreased NO contributes to hypertension, atherosclerosis, and diabetes (column 1, lines 56-60). Garfield teaches that various N-nitroso-N-substituted hydroxylamines can be used as NO donors to treat these diseases. Additionally, Garfield teaches that suitable pharmaceutically acceptable carriers include vegetable oils, polyethylene glycol, and hydroxypropyl methylcellulose and that fats (vegetable oils) may be used as carriers utilizing microencapsulation (column 9, lines 4-32). These properties of fats render obvious the use of lipids in combination with NO. Garfield also teaches that the compounds capable of donating NO have a structure wherein the functional group is equal to that of claim 68, and more specifically claim 69 of the instant application (column 4, lines 30-47) wherein the R group is a steroid, or a biologically active moiety designed to target the NO releasing agent to a specific organ or tissue (column 5, lines 18-25).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Stamler and Garfield to obtain a drug delivery system which comprises a medical article and a lipid molecule comprising a N-nitroso, O-nitroso, or S-nitroso functional group which is capable of delivering NO to a patient. Garfield teaches to attach a NO donating group (as in claims 68 and 69 of the instant) to a steroid, which is a lipid. One of ordinary skill in the art would have a reasonable expectation of success in using other members of the same class of compounds as the R group of Garfield, as it is the art recognized -N-N=O moiety which provides the function of releasing the therapeutically effective NO group. One would be motivated to use lipids as the R group because lipids are known to form liposomes, wherein an additional active agent could be entrapped in the liposome which would

Applicants argue that the prior Office Action concludes that the deficiency that Stamler lacks, the use of lipids in medical articles as NO releasing agents, is addressed by the teachings of Garfield. However, as set forth supra, Garfield teaches that vegetable oils, fats, and steroids can be used as NO carriers, or NO releasing agents. Stamler teaches to coat medical devices in agents which will release NO. Stamler lacks the teaching of a lipid based NO delivery system and teaches of NO coated medical articles. Garfield teaches vegetable oil, fat, and steroid based NO delivery systems, but lacks the teaching of incorporating into/onto a medical device.

Applicants argue that there is no motivation to provide an additional active agent as the examiner asserts. Column 9, lines 41-43 of Garfield states "The agents or combination can be administered as an admixture with any other active agent...".

Applicants argue that there is no motivation to use lipid molecules that have NO molecules as NO donating molecules. However, Garfield teaches the use of vegetable oils, fats, and column 5, lines 20-23 state, "in a preferred embodiment, R is a biologically active moiety (a steroid) designed to target the NO releasing agent to a specific organ or tissue...". Steroids are known to be lipids, and thus a NO group on a lipid is known.

Applicants argue that there is no motivation to use a hydrophobic lipid molecule versus the hydrophilic polymer molecules known in the art. Stamler teach that hydrophobic molecules can be used (column 3, lines 55-56).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so

time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Claims 33-48, 50-54, 56 and 58-70 rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler and Garfield as applied to claims 33-48, 50-52, 56 and 58-70 above, and further in view of Green et al. (Green) (US Patent 5,814,666).

The claims of the instant application are drawn to the drug delivery system as set forth supra, and additionally to a method of treating cancer or bacterial infections, or warts (a papova-type viral infection).

Stamler and Garfield teach the drug delivery system as set forth supra, what is not taught is to use the drug delivery system to treat cancer or bacterial infections or warts.

Green teaches to use liposomes containing nitric oxide donors to treat macrophage-based diseases caused by viruses, bacteria, fungi, and parasites (column 4, lines 63-65).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the drug delivery system as taught by Stamler and Garfield to treat the diseases as taught by Green because Green teaches the disease is treated by a nitric oxide donating complex. One would be motivated to use the system of Stamler and Garfield because the lipids would form into a liposome as indicated by Green, and comprise the nitric oxide releasing group (N-, O-, or S-nitroso group) in the complex.

Claims 33-48, 50-52, 55, 56 and 58-70 rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler and Garfield as applied to claims 33-48, 50-52, 56 and 58-70 above, and further in view of Smith et al. (Smith) (US Patent 5,519,020).

The claims of the instant application are drawn to the drug delivery system as set forth supra, and additionally to a method of promoting wound healing in a patient.

Stamler and Garfield teach the drug delivery system as set forth supra, what is not taught is to use the drug delivery system as a method of promoting wound healing in a patient.

Smith teaches to use a controlled release NO releasing compound to promote wound healing in a patient (column 3, lines 55-57).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the drug delivery system as taught by Stamler and Garfield to promote wound healing as taught by Smith because Smith teaches that wound healing is accelerated by a nitric oxide. One would be motivated to use the system of Stamler and Garfield because the lipids would form into a liposome and have the capability of comprising an additional active agent, as well as comprising the nitric oxide releasing group (N-, O-, or S-nitroso group) in the complex.

Applicants argue that the Green and Smith references do not teach the deficiencies of Stamler and Garfield. However, Smith and Green are cited to show that the various disorders are all known to be treated by NO releasing compounds.

It is noted that the Examiner has included page 233 of Bettelheim, Brown, and March's

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss C McIntosh whose telephone number is 703-308-9479. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James O. Wilson
Supervisory Patent Examiner
Art Unit 1623

Traviss C. McIntosh
August 6, 2003